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Request for grant of a patent

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1.	Your reference **GB Case**	**4-30754/P1/HO 12**
2.	Patent application number *(The Patent Office will fill in this part)*	**9828340.1**
3.	Full name, address and postcode of the or of each applicant *(underline all surnames)*	**NOVARTIS AG** **SCHWARZWALDALLEE 215** **4058 BASEL** **SWITZERLAND**
	Patent ADP number *(if you know it)*	712547 7002
	If the applicant is a corporate body, give the country/state of its incorporation	**SWITZERLAND**
4.	Title of invention	**ORGANIC COMPOUNDS**
5.	Name of your agent *(If you have one)*	
	"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*	**B.A. YORKE & CO.** **CHARTERED PATENT AGENTS** **COOMB HOUSE, 7 ST. JOHN'S ROAD** **ISLEWORTH** **MIDDLESEX TW7 6NH**
	Patents ADP number *(if you know it)*	**1800001**

6.	If you are declaring priority from one ore more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number	Country	Priority application number *(if you know it)*	Date of filing (day/month/year)

7.	If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application	Number of earlier application	Date of filing (day/month/year)

8.	Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*	**YES**
	a) any applicant named in part 3 is not an inventor, or	
	b) there is an inventor who is not named as an applicant, or	
	c) any named applicant is a corporate body.	
	(see note (d))	

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Continuation sheets of this form	
Description	12
Claim(s)	2
Abstract	
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10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	1
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application

Signature Date

B.A. Yorke & Co. 22.12.98

12. Name and daytime telephone number of person to contact in the United Kingdom

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Organic Compounds

This invention relates to the use of organic compounds in inhalable form for the preparation of a medicament for the treatment of sexual dysfunction, including male erectile dysfunction and female sexual dysfunction.

WO 94/28902, WO 96/16644 and WO 96/16657 describe the use of selective inhibitors of cyclic guanosine 3',5'-monophosphate phosphodiesterases (cGMP PDEs), particularly cGMP PDE 5 inhibitors, in the treatment of sexual dysfunction. These references state that, for human use, the inhibitors are administered orally or, where the recipient suffers from a swallowing disorder or from impairment of drug absorption after oral administration, parenterally, sublingual and buccal administration being suggested as means of parenteral administration.

It has now surprisingly been found that compounds effective in the treatment, i.e. curative or prophylactic treatment, of sexual dysfunction exhibit maximum concentration in plasma in a very short time following administration by inhalation, indicating a more rapid onset of action for the compounds when administered by this route.

Accordingly, the present invention provides, in one aspect, the use of an inhalable form of a compound effective in the treatment of sexual dysfunction for the preparation of an inhalable medicament for the treatment of sexual dysfunction.

In another aspect, the invention provides a method of treating sexual dysfunction which comprises administering by inhalation a compound effective for such treatment to a subject in need of such treatment.

In further aspects, the invention provides

(a) an inhibitor of cGMP PDE, particularly cGMP PDE 5, in inhalable form for use in the treatment of sexual dysfunction; and

(b) the use of an inhibitor of cGMP PDE, particularly cGMP PDE 5, in inhalable form for the preparation of an inhalable medicament for the treatment of sexual dysfunction.

The compound effective in the treatment of sexual dysfunction may be a cGMP PDE inhibitor, preferably a cGMP PDE 5 inhibitor, such as a pyrazolopyrimidinone or an aminoquinazoline derivative. Examples of such inhibitors include:

a pyrazolopyrimidinone as disclosed in EP-A-0463756, EP-A-0526004, WO 94/28902, WO 96/16657 or WO 98/49166;
a 5-substituted pyrazole [4,3-d]pyrimidin-7-one as disclosed in EP-A-0201188;
a griseolic acid derivative as disclosed in EP-A-0214708 and EP-A-0319050;
a 2-phenylpurinone derivative as disclosed in EP-A-0293063;
a phenylpyridone derivative as disclosed in EP-A-0347027;
a fused pyrimidine derivative as disclosed in EP-A-0347146;
a condensed pyrimidine derivative as disclosed in EP-A-0349239;
a pyrimidopyrimidine derivative as disclosed in EP-A-0351058;
a purine compound as disclosed in EP-A-0352960;
a quinazolinone derivative as disclosed in EP-A-0371731;
a phenylpyrimidone derivative as disclosed in EP-A-0395328;
an imidazoquinoxalinone derivative or its aza analogue as disclosed in EP-A-0400583;
a phenylpyrimidone derivative as disclosed in EP-A-0400799;
a phenylpyridone derivative as disclosed in EP-A-0428268;
a pyrimidopyrimidine derivative as disclosed in EP-A-0442204;
a 4-aminoquinazoline derivative as disclosed in EP-A-0579496;
a 4,5-dihydro-4-oxo-pyrrolo[1,2-a]quinoxaline derivative or its aza analogue as disclosed in EP-A-0584487;
a polycyclic guanine derivative as disclosed in WO91/19717;
a nitrogenous heterocyclic compound as disclosed in WO93/07124;
a 2-benzyl-polycyclic guanine derivative as disclosed in WO94/19351;
a quinazoline derivative as disclosed in US4060615;
a 6-heterocyclyl pyrazolo [3,4-d]pyrimidin-4-one as disclosed in US5294612;
a benzimidazole as disclosed in Japanese Kokai 5-222000;
a cycloheptimidazole as disclosed in European Journal of Pharmacology, 251, (1994), 1.
a N-containing heterocycle as disclosed in WO94/22855;
a pyrazolopyrimidine derivative as disclosed in EP-A-0636626;
a 4-aminopyrimidine derivative as disclosed in EP-A-0640599;
an imidazoquinazoline derivative as disclosed in EP-A-0668280;
an anthranilic acid derivative as disclosed in EP-A-0686625;
a 4-aminoquinazoline derivative as disclosed in US5436233;

a tetracyclic derivative as disclosed in WO95/19978;
a quinazoline compound as disclosed in EP-A-0669324;
a fused pyridazine compound as disclosed in EP-A-0722936;
an imidazoquinoline compound as disclosed in EP-A-0758653;
a substituted pyrazoloquinolinamine as disclosed in WO96/28159;
a substituted pyrazolopyrimidinone as disclosed in WO96/28429;
an indole derivative as disclosed in WO96/32379; or
a benzimidazole derivative as disclosed in WO97/03070.

The invention includes the use of any compound within the scope of the claims of the patent specifications listed above, particularly the specific compounds disclosed in those specifications, more particularly the specific compounds disclosed in the Examples and claims of those specifications.

Other compounds effective in the treatment of sexual dysfunction include adrenoreceptor blocking agents such as phentolamine methanesulphonate (mesilate) which may be prepared by condensation of N-(3-hydroxyphenyl)-N-(4-methylphenyl)amine with 2-(chloromethyl)-4,5-dihydro-1H-imidazole by heating at 150-160°C either without solvent as described in US2503059 or in o-dichlorobenzene as described by E.Urech et al, Helv Chim Acta 1950, 33, 1386-407.

Preferred compounds for use in the present invention include pyrazolopyrimidinone cGMP PDE 5 inhibitors as disclosed in WO94/28902, more preferably

5-(2-ethoxy-5-morpholinoacetylphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
5-(5-morpholinoacetyl-2-n-propoxyphenyl)-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
5-[2-ethoxy-5-(4-methyl-1-piperazinylsulphonyl)-phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
5-[2-allyloxy-5-(4-methyl-1-piperazinylsulphonyl)-phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
5-[2-ethoxy-5-[4-(2-propyl)-1-piperazinyl-sulphonyl]phenyl}-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
5-[2-ethoxy-5-[4-(2-hydroxyethyl)-1-piperazinyl-sulphonyl]phenyl}-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

5-{5-[4-(2-hydroxyethyl)-1-piperazinylsulphonyl]-2-n-propoxyphenyl}-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
5-[2-ethoxy-5-(4-methyl-1-piperazinylcarbonyl)-phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
and 5-[2-ethoxy-5-(1-methyl-2-imidazolyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo{4,3-d]pyrimidin-7-one.

Other preferred compounds for use in the present invention include pyrazolopyrimidinone and quinazolinone cGMP PDE 5 inhibitors as disclosed in WO96/16657, more preferably

1-ethyl-5-[5-(n-hexylsulphamoyl)-2-n-propoxyphenyl]-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
1-ethyl-5-(5-diethylsulphamoyl-2-n-propoxyphenyl)-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]-pyrimidin-7-one;
5-[5-(N-cyclohexylmethyl-N-methylsulphamoyl)-2-n-propoxyphenyl]-1-ethyl-3-methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
6-(5-bromo-2-n-propoxyphenyl)-3-methyl-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;
3-methyl-6-(5-morpholinosulphonyl-2-n-propoxyphenyl)-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;
6-[5-(2-carboxyvinyl)-2-n-propoxyphenyl]-3-methyl-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;
6-[5-(2-t-butoxycarbonylvinyl)-2-n-propoxyphenyl]-3-methyl-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;
3-methyl-6-[5-(2-morpholinocarbonylvinyl)-2-n-propoxyphenyl]-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;
3-methyl-6-[5-(2-morpholinocarbonylethyl)-2-n-propoxyphenyl]-1-n-propyl-1,5-dihydro-4H-pyrazolo[3,4-d]pyrimidin-4-one;
2-{2-ethoxy-5-[4-(2-hydroxyethyl)-1-piperazinylsulphonyl]phenyl}-8-methylquinazolin-4-(3H)-one;
2-{5-[4-(2-hydroxyethyl)-1-piperazinylsulphonyl]-2-n-propoxyphenyl}-8-methylquinazolin-4(3H)-one;
8-methyl-2-{5-[2-(4-methyl-1-piperazinylcarbonyl)-ethenyl]-2-n-propoxyphenyl}quinazolin-4(3H)-one;
8-carbamoyl-2-{2-ethoxy-5-[4-(2-hydroxyethyl)-1-piperazinylsulphonyl]phenyl}quinazolin-4(3H)-one;

8-ethylcarbamoyl-2-(2-n-propoxyphenyl)quinazolin-4(3H)-one;
2-[2-ethoxy-5-(4-ethoxycarbonylpiperidino-sulphonyl)phenyl]-8-n-propylpyrido[3,2-d]pyrimidin-4(3H)-one;
2-[5-(4-carboxypiperidinosulphonyl)-2-ethoxyphenyl]-8-n-propylpyrido[3,2-d]pyrimidin-4(3H)-one;
2-{2-ethoxy-5-[4-(2-hydroxyethyl)-1-piperazinyl-sulphonyl]phenyl}-8-n-propylpyrido[3,2-d]pyrimidin-4(3H)-one;
and 2-{2-ethoxy-5-[(bis-3-pyridylsulphonyl)amino]-phenyl}-8-n-propylpyrido[3,2-d]pyrimidin-4(3H)-one.

Other preferred compounds for use in the present invention include pyrazolopyrimidinone cGMP PDE5 inhibitors as disclosed in WO98/49166, more preferably

5-{5-[4-(2-hydroxyethyl)piperazin-1-ylsulphonyl]-2-n-propoxyphenyl}-3-n-propyl-1-(pyridin-2-yl)methyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
1-(1-methylimidazol-2-yl)methyl-5-[5-(4-methylpiperazin-1-sulphonyl)-2-n-propoxyphenyl]-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
5-{5-[4-(2-hydroxyethyl)piperazin-1-ylsulphonyl]-2-n-propoxyphenyl}-3-n-propyl-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
5-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-n-propoxyphenyl]-3-n-propyl-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
3-ethyl-5-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-n-propoxyphenyl]-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
5-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-n-propoxyphenyl]-3-n-propyl-2-(pyridazin-3-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
5-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-n-propoxyphenyl]-3-n-propyl-2-(pyridazin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one; and
5-[2-ethoxy-5-(4-ethylpiperazin-1-ylsulphonyl)phenyl]-3-n-propyl-2-(pyridin-2-yl)methyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
5-[5-(4-methylpiperazin-1-ylsulphonyl)-2-n-propoxyphenyl]-1-(1-methyl-1,2,4-triazol-5-yl)methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
5-[5-(4-methylpiperazin-1-ylsulphonyl)-2-n-propoxyphenyl]-2-(1-methyl-1,2,4-triazol-5-yl)methyl-3-n-propyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
1-benzyl-5-[2-ethoxy-5-(4-methylpiperazin-1-ylsulphonyl)phenyl]-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

2-benzyl-5-[2-ethoxy-5-(4-methylpiperazin-1-sulphonyl)phenyl]-3-n-propyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
5-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-n-propoxyphenyl]-1-(2-morpholin-4-ylethyl)-3-n-propyl-1,6-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
5-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-n-propoxyphenyl]-2-(2-morphin-4-ylethyl)-3-n-propyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
5-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-n-propoxyphenyl]-2-(2-methanesulphonamidophenyl)-3-n-propyl-2,6-dihydro-7H-pyrazolo[4,3-d]-pyrimidin-7-one;
5-[5-(4-methylpiperazin-1-ylsulphonyl)-2-n-propoxyphenyl]-3-n-propyl-2-pyrimidin-2-yl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
2-cyclobutylmethyl-5-[2-ethoxy-5-(4-methylpiperazin-1-ylsulphonyl)phenyl]-3-n-propyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;
5-[5-(4-ethylpiperazin-1-ylsulphonyl)-2-n-propoxyphenyl]-2-(1-oxidopyridin-2-yl)methyl-3-n-propyl-2,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one;

Further preferred compounds for use in the present invention include

4-aminoquinazoline derivatives as disclosed in US5436233, more preferably 4-phenylmethylamino-2-((1-imidazolyl)methyl)-quinazoline, 4-phenylmethylamino-2-((1-imidazolyl)methyl)-quinazoline, 6-chloro-4-phenylmethylamino-2-(1-imidazolylmethyl)quinazoline, 6-chloro-4-phenylamino-2-(1-imidazolylmethyl)-quinazoline, 6-chloro-4-(3-carboxyphenyl)amino-2-(1-imidazolylmethyl)quinazoline, 4-phenylmethylamino-2-(2-(3-pyridyl)vinyl)quinazoline, 4-phenylmethylamino-6-chloro-2-(1-imidazolyl)quinazoline and 4-phenylmethylamino-6-chloro-2-(3-pyridyl)quinazoline;
pyrazolopyrimidine derivatives as disclosed in EP0636626, more preferably
1,3-dimethyl-6-(2-propoxy-5-acetamidophenyl)-1,5-dihydropyrazolo[3,4-d]pyrimidin-4-one;
1-ethyl-3-methyl-6-[2-propoxy-5-(4-methyl-2-thiazolyl)phenyl]-1,5-dihyropyrazolo[3,4-d]pyrimidin-4-one;
1-ethyl-3-methyl-6-[2-propoxy-5-(2-methyl-4-thiazolyl)phenyl]-1,5-dihyropyrazolo[3,4-d]pyrimidin-4-one;
1-ethyl-3-methyl-6-[2-propoxy-5-(2-(3-pyridyl)-4-thiazolyl)phenyl]-1,5-dihydropyrazolo[3,4-d]pyrimidin-4-one;
1,3-dimethyl-6-(2-propoxy-5-(2-methyl-4-thiazolyl)phenyl]-1,5-dihydropyrazolo[3,4-d]pyrimidin-4-one;
1,3-dimethyl-6-(2-propoxy-5-(3-phenyl-1,2,4-triazol-5-yl)phenyl]-1,5-dihydropyrazolo[3,4-d]pyrimidin-4-one;

1,3-dimethyl-6-(2-propoxy-5-methanesulfonamidophenyl)-1,5-dihydro-pyrazolo[3,4-d]pyrimidin-4-one;
pharmaceutically acceptable salts and solvates (e.g. hydrates) of such pyrazolopyrimidines;
arylpyrazolopyrimidinones as disclosed in WO96/28448, more preferably
1-cyclopentyl-3-ethyl-6-(2-propoxyphenyl)pyrazolo[3,4-d]pyrimidin-4-one,
1-cyclopentyl-3-ethyl-6-[4-(1-imidazolyl)phenyl]pyrazolo[3,4-d]pyrimidin-4-one,
1-cyclopentyl-3-ethyl-6-[3-(2-(4-morpholinyl)ethoxy)phenyl]pyrazolo[3,4-d]pyrimidin-4-one,
1-cyclopentyl-3-ethyl-6-[2-ethoxy-4-(1-imidazolyl)phenyl]pyrazolo[3,4-d]pyrimidin-4-one, and
1-cyclopentyl-3-ethyl-6-[2-(CH_2=$CHCH_2O$)phenyl]pyrazolo[3,4-d] pyrimidin-4-one; and
6-heterocyclyl-pyrazolo[3,4-d]pyrimidin-4-ones as disclosed in US5294612, more preferably
1-tert-butyl-3-(3,4-dimethoxybenzyl)-6-(4-pyridyl)-pyrazolo[3,4-d]pyrimidin-4-one,
1-cyclopentyl-3-methyl-6-(4-quinolinyl)-pyrazolo[3,4-d]pyrimidin-4-one,
1-cyclopentyl-3-methyl-6-(6-quinolinyl)-pyrazolo[3,4-d]pyrimidin-4-one,
1-cyclopentyl-3-ethyl-6-(4-pyridyl)-pyrazolo[3,4-d]pyrimidin-4-one,
1-cyclopentyl-3-methyl-6-(4-pyridyl)-pyrazolo[3,4-d]pyrimidin-4-one,
1-tert-butyl-3-benzyl-6-(4-pyridyl)-pyrazolo[3,4-d]pyrimidin-4-one,
1-tert-butyl-3-methyl-6-(4-pyridyl)-pyrazolo[3,4-d]pyrimidin-4-one,
1-cyclopentyl-3-methyl-6-(3-pyridyl)-pyrazolo[3,4-d]pyrimidin-4-one,
1-cyclopentyl-3-ethyl-6-(3-ethoxy-4-pyridyl)-pyrazolo[3,4-d]pyrimidin-4-one,
1-tert-butyl-3-pyridylmethyl-6-(4-pyridyl)-pyrazolo[3,4-d]pyrimidin-4-one,
1-cyclopentyl-3-ethyl-6-[2-(4-morpholinyl)ethoxy-4-pyridyl)-pyrazolo[3,4-d]pyrimidin-4-one,
1-cyclopentyl-3-trifluoromethyl-6-(3-ethoxy-4-pyridyl)-pyrazolo[3,4-d]pyrimidin-4-one,
1-cyclopentyl-3-ethyl-6-(3-methoxy-4-pyridyl)-pyrazolo[3,4-d]pyrimidin-4-one and
1-cyclopentyl-3-ethyl-6-(3-sec-butoxy-4-pyridyl)-pyrazolo[3,4-d]pyrimidin-4-one

Especially preferred compounds for use in the invention include 5-[2-ethoxy-5-(4-methylpiperazinylsulfonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one, 4-phenylmethylamino-6-chloro-2-(1-imidazolyl)quinazoline, 4-phenylmethylamino-6-chloro-2-(3-pyridyl)quinazoline, 1,3-dimethyl-6-(2-propoxy-5-methanesulfonylamidophenyl)-1,5-dihydropyrazolo[3,4-d]pyrimidin-4-one and 1-cyclopentyl-3-ethyl-6-(3-ethoxy-4-pyridyl)-pyrazolo[3,4-d]pyrimidin-4-one.

In a yet further aspect, the invention provides a medicament comprising a cGMP PDE inhibitor as disclosed in WO94/28902, WO96/16657, WO98/49166, EP-A-0636626 or US5436233, particularly the preferred and especially preferred such inhibitors as described above, in inhalable form.

The inhalable form of the medicament effective for the treatment of sexual dysfunction may be, for example, an atomisable composition such as an aerosol comprising the active ingredient in solution or dispersion in a propellant or a nebulizable composition comprising a dispersion of the active ingredient in an aqueous, organic or aqueous/organic medium, or a finely divided particulate form comprising the active ingredient in finely divided form optionally together with a pharmaceutically acceptable carrier in finely divided form.

An aerosol composition suitable for use as the inhalable form of the medicament may comprise the active ingredient, for example a cGMP PDE inhibitor as disclosed in WO94/28902, WO96/16657, WO98/49166, EP-A-0636626 or US5436233, in solution or dispersion in a propellant, which may be chosen from any of the propellants known in the art. Suitable such propellants include hydrocarbons such as n-propane, n-butane or isobutane or mixtures of two or more such hydrocarbons, and halogen-substituted hydrocarbons, for example fluorine-substituted methanes, ethanes, propanes, butanes, cyclopropanes or cyclobutanes, particularly 1,1,1,2-tetrafluoroethane (HFA134a) and heptafluoropropane (HFA227), or mixtures of two or more such halogen-substituted hydrocarbons. Where the active ingredient is present in dispersion in the propellant, i.e. where it is present in particulate form dispersed in the propellant, the aerosol composition may also contain a lubricant and a surfactant, which may be chosen from those lubricants and surfactants known in the art. The aerosol composition may contain up to about 5% by weight, for example 0.002 to 5%, 0.01 to 3%, 0.015 to 2%, 0.1 to 2%, 0.5 to 2% or 0.5 to 1%, by weight of the active ingredient, based on the weight of the propellant. Where present, the lubricant and surfactant may be in an amount up to 5% and 0.5% respectively by weight of the aerosol composition. The aerosol composition may also contain ethanol as co-solvent in an amount up to 30% by weight of the composition, particularly for administration from a pressurised metered dose inhalation device.

A finely divided particulate form, i.e. a dry powder, suitable for use as the inhalable form of the medicament may comprise the active ingredient, for example a cGMP PDE inhibitor as disclosed in WO94/28902, WO96/16657, WO98/49166, EP-A-0636626 or US5436233, in finely divided particulate form, optionally together with a finely divided particulate carrier,

which may be chosen from materials known as carriers in dry powder inhalation compositions, for example saccharides, including monosaccharides, disaccharides and polysaccharides such as arabinose, glucose, fructose, ribose, mannose, sucrose, lactose, maltose, starches or dextran. As especially preferred carrier is lactose. The dry powder may be in capsules of gelatin or plastic, or in blisters, for use in a dry powder inhalation device, preferably in dosage units of 5 μg to 40 mg of the active ingredient. Alternatively, the dry powder may be contained as a reservoir in a multi-dose dry powder inhalation device.

In the finely divided particulate form of the medicament, and in the aerosol composition where the active ingredient is present in particulate form, the active ingredient may have an average particle diameter of up to about 10 μm, for example 0.1 to 5 μm, preferably 1 to 5 μm. The particle size of the active ingredient, and that of a solid carrier where present in dry powder compositions, can be reduced to the desired level by conventional methods, for example by grinding in an air-jet mill, ball mill or vibrator mill, microprecipitation, spray-drying, lyophilisation or recrystallisation from supercritical media.

The inhalable medicament may be administered using an inhalation device suitable for the inhalable form, such devices being well known in the art. Accordingly, the invention also provides a pharmaceutical product comprising a cGMP PDE inhibitor as disclosed in WO94/28902, WO96/16657, WO98/49166, EP-A-0636626 or US5436233 in inhalable form as hereinbefore described in association with an inhalation device. In a further aspect, the invention provides an inhalation device containing a cGMP PDE inhibitor as disclosed in WO94/28902, WO96/16657, WO98/49166, EP-A-0636626 or US5436233 in inhalable form as hereinbefore described.

Where the inhalable form of the active ingredient is an aerosol composition, the inhalation device may be an aerosol vial provided with a valve adapted to deliver a metered dose, such as 10 to 100 μl, e.g. 25 to 50 μl, of the composition, i.e. a device known as a metered dose inhaler. Suitable such aerosol vials and procedures for containing within them aerosol compositions under pressure are well known to those skilled in the art of inhalation therapy. Where the inhalable form of the active ingredient is a nebulizable aqueous, organic or aqueous/organic dispersion, the inhalation device may be a known nebulizer, for example a conventional pneumatic nebulizer such as an airjet nebulizer, or an ultrasonic nebulizer, which may contain, for example, from 1 to 50 ml, commonly 1 to 10 ml, of the dispersion; or a hand-held nebulizer such as an AERx (ex Aradigm, US) or BINEB (Boehringer

Ingelheim) nebulizer which allows much smaller nebulized volumes, e.g. 10 to 100 µl, than conventional nebulizers. Where the inhalable form of the active ingredient is the finely divided particulate form, the inhalation device may be, for example, a dry powder inhalation device adapted to deliver dry powder from a capsule or blister containing a dosage unit of the dry powder or a multidose dry powder inhalation device adapted to deliver, for example, 25 mg of dry powder per actuation. Suitable such dry powder inhalation devices are well known.

The invention is illustrated by the following Example.

Example

The absorption time for 5-[2-ethoxy-5-(4-methylpiperazinylsulfonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one, hereinafter Compound A, following administration by inhalation is measured in a rodent pharmacokinetic model which simulates inhalation as a route of administration. Male Wistar:Han rats used for this model are supplied by Harlan UK Ltd at 105 days of age and approximately 350g weight. They are fed ad libitum with a standard laboratory diet and housed under controlled conditions (12 hours light/dark cycle; 20°C) for at least one week prior to the experiment.

Compound A is dissolved, at a concentration of 1.75 mg/ml in 0.9% saline which has been acidified with 1M aqueous HCl (5 µl), giving a clear solution of pH 5.0. To the solution is added 1M aqueous NaOH (2µl) to increase the pH to 6.0, resulting in a very fine suspension. The suspension is administered to the rats directly into the trachea via the mouth and vocal chords from a 1.0 ml plastic syringe and Penn-Century microsprayer. Each animal receives a 2.1 µmol/kg dose in 200 µl of suspension.

The following surgical procedure is used to prepare the animals for the experiment: the animals are anaesthetised, initially with 4% halothane, maintained with 2% halothane, both in a 1:1 oxygen: nitrous oxide mixture carrier. The anaesthetised animals are shaved on their ventral neck and craniodorsal back, then swabbed with a solution of 5% Hibitane in a 70% solution of ethanol in water. A 10 mm longitudinal incision is made in the ventral neck, the connective tissue, salivary glands, omohyoideus and sternohyoideus muscle are separated by blunt dissection and the left common carotid artery is exposed, cleared of the Vagus nerve and then elevated. The carotid artery is clipped and cannulated with a 150 mm

length of pp50 Portex tubing attached to a 1 ml syringe with a 26G blunt needle filled with heparinised saline (500 i.u./ml in 0.9% saline). 10 mm of cannula is inserted, tied in place using braided silk sutures proximal and distal to the insertion point, and the clip is removed. A 2 mm incision and subcutaneous tunnel is made in the craniodorsal neck between the scapula with a 100 mm 16G curved gavage needle emerging adjacent to the cannulation site and right salivary gland. The cannula is clamped 20 mm above the insertion point with artery forceps covered with polythene tubing to avoid damaging the cannula. The syringe and needle are removed from the cannula and the free end passed through the gavage needle. The gavage needle is withdrawn and the syringe and needle are replaced on the cannula. The forceps are removed and the cannula is further withdrawn to form a gentle curve across the trachea, allowing the incision to be closed without interference, enabling free blood flow to be tested by drawing back the syringe. 50 µl of heparinised saline is administered. The ventral incision is dusted with Cicatrin antibiotic powder (Wellcome, Greenford, UK) and closed with Michel clips (12 mm x 2.5 mm). A small suture loop is formed 10 mm distal to the cannula exit point and the exteriorised cannula tied to it so that it lies along the midline of the back. The cannula is again tested for free blood flow and a further 50 µl of heparinised saline is administered. The cannula is clamped with modified artery forceps near to the securing suture and cut to a length of 20 mm. A dressmakers pin is inserted to seal the cannula and the forceps are removed. Buprenorphine (Vetergesic, Reckitt and Colman) is administered (0.06 mg/kg i.m.) and the animals are placed in cages over a heated pad until fully ambulatory. Thereafter, they are placed in metabolism cages with free access to food and water. The patency of the cannula is assessed 6 hours after the operation and again immediately before experimentation.

At 0 min, i.e. prior to dosing with Compound A, a 300 µl sample of blood is collected from the cannula into a 2.0 ml plastic syringe containing 60 µl aqueous 3.8% tri-sodium citrate. Samples are immediately transferred to a 1.9 ml Eppendorf tube and held on ice. Serial blood samples are withdrawn at ten time intervals up to 1440 minutes after dosing with Compound A. At each time point, the withdrawn blood sample is replaced with an equal volume of heparinised saline (10 i.u./ml in 0.9% saline). After the final blood sample, the rats are killed by an overdose of sodium pentobarbitone (Sagatal, Rhone Merieux, UK), followed by cervical dislocation.

Withdrawn blood samples are analysed as follows:

Chilled whole blood samples are centrifuged at 11,000 rpm (Hereaus Biofuge 15) for 6 minutes and the plasma supernatant collected. The plasma (100 µl) is placed into an extraction tube containing acetonitrile (300 µl). After shaking for 10 minutes and centrifuging for 12 minutes, 200 µl of supernatant is transferred from the extraction tube to an autosampler vial and diluted with water (200 µl). The resulting sample is analysed by LC-MS/MS (liquid chromatography - tandem mass spectrometry). Calibration samples are prepared by adding 1 µl of a 10 mM solution of Compound A in dimethyl sulfoxide to 2 ml of blank rat plasma to give a 5 µM plasma standard, and diluting this plasma standard with blank plasma to give final concentrations of 1.67 µM, 0.56 µM, 0.19 µM, 0.062 µM, 0.021 µM and 0.007 µM. Validation samples are prepared by appropriate dilution of the 5 µM plasma standard with blank rat plasma to give concentrations of 1, 0.5, 0.2, 0.1 and 0.05 µM. The calibration standard samples are analysed by LC-MS/MS as for the withdrawn plasma samples. Calibration curves ($y = mx + b$), represented by the plots of the peak area ratios (y) of Compound A versus the concentrations (x) of the calibration samples, are generated using weighted (1/x) linear least-squares regression as the mathematical model. Concentrations in the withdrawn, calibration and validation samples are calculated from the resulting peak areas and the regression equation of the calibration curve. Pharmacokinetic parameters are calculated by Win Nonlin (Professional version 1.5) using non-compartmental analysis. The results (mean for 6 animals) give a Tmax of 5 minutes, i.e. the concentration of Compound A in plasma reaches a maximum within 5 minutes after intratracheal administration.

Claims

1. The use of an inhalable form of a compound effective in the treatment of sexual dysfunction for the preparation of an inhalable medicament for the treatment of sexual dysfunction.

2. Use according to claim 1, in which said compound is an inhibitor of cGMP PDE, particularly cGMP PDE 5.

3. Use according to claim 2, in which said inhibitor is a pyrazolopyrimidinone or an aminoquinazoline derivative.

4. Use according to claim 3, in which said inhibitor is a pyrazolopyrimidinone as disclosed in published International Patent Application No. WO94/28902, WO96/16657 or WO98/49166 or published European Patent Application No EP-A-0636626, a 4-aminoquinazoline derivative as disclosed in US Patent No. 5436233, an arylpyrazolopyrimidinone as disclosed in published International Patent Application No. WO96/28448 or a 6-heterocyclyl-pyrazolo[3,4-d]pyrimidin-4-one as disclosed in US Patent 5294612.

5. Use according to claim 4, in which said inhibitor is 5-[2-ethoxy-5-(4-methylpiperazinylsulfonyl)phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one, 4-phenylmethylamino-6-chloro-2-(1-imidazolyl)quinazoline, 4-phenylmethylamino-6-chloro-2-(3-pyridyl)quinazoline, 1,3-dimethyl-6-(2-propoxy-5-methanesulfonylamidophenyl)-1,5-dihydropyrazolo[3,4-d]pyrimidin-4-one or 1-cyclopentyl-3-ethyl-6-(3-ethoxy-4-pyridyl)-pyrazolo[3,4-d]pyrimidin-4-one.

6. Use according to any one of the preceding claims, in which the inhalable form of said medicament is an atomisable composition or a finely divided particulate form.

7. Use according to claim 6, in which said inhalable form is an aerosol comprising said compound in solution or dispersion in a propellant or a nebulizable composition comprising a dispersion of said compound in an aqueous or aqueous/organic medium.

8. Use according to claim 6, in which said inhalable form is a finely divided particulate form comprising said compound in finely divided particulate form, optionally together with a finely divided particulate carrier.

9. A medicament comprising a cGMP PDE inhibitor as disclosed in WO94/28902, WO96/16657, WO98/49166, EP-A-0636626 or US5436233 in inhalable form.

10. A medicament according to claim 9, in which the inhalable form is as specified in any one of claims 6 to 8.

11. A pharmaceutical product comprising a pyrazolopyrimidinone as specified in claim 9 or 10 in association with an inhalation device.

12. An inhalation device containing a pyrazolopyrimidinone as specified in claim 9 or 10.